AMENDMENTS AND UPDATES TO
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
JUNE 14, 1999

February 11, 1999 (letter date)	**9810-267 Morris**	**A Phase I Study of Intralesional Administration of an Adenovirus Vector Expressing the HSV-1 Thymidine Kinase Gene (AdV.RSV-TK) in Combination with Escalating Doses of Ganciclovir in Patients with Cutaneous Metastatic Malignant Melanoma** **Amendments:** 1) Viral dose will now be given in particles instead of plaque forming units. No change has been made in the absolute amount of adenovirus that will be administered. 2) Ganciclovir will be administered every 12 hours, instead of twice-a-day (with only an eight hour interval). 3) Method for measuring blood ganciclovir levels and pharmacokinetics was changed.
February 12, 1999	**9707-200 Levy**	**A Phase I/II Study of Vaccine Therapy for B-Cell Lymphoma Utilizing Plasmid DNA Coding for Tumor Idiotype** **Amendment:** All patients at each of the three dose levels (200 mg, 600 mg, or 1800 mg) are eligible for re-treatment at the highest dose (1800 mg) as long as they are either in clinical remission o have minimal/moderate residual disease. The objective is to maximize any immune response. The re-treatment will be performed by both intradermal and intramuscular injection. **Update:**

		To date, a total of ten patients have been treated. Four at the lowest dose, four at the middle dose, and two at the highest dose. None of the lower dose patients, who have been evaluated, have demonstrated an anti-idiotype immune response.
February 16, 1999	**9701-172 Cornetta and Abonour**	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study** **Update:** Accrual goal is 15 patients that receive transduced peripheral blood stem cells. To date, 12 patients have been enrolled and 11 of the 12 have received both non-transduced and transduced mobilized peripheral blood stem cells. One patient did not mobilize a sufficient number of cells for transduction; this patient received two infusions of non-transduced cells. The transgene has been detected by PCR in all 11 patients that received transduced cells; gene transfer into progenitor cells ranged from 5 to 52%. All samples analyzed for replication competent virus have been negative. At one and six months post-transplant, bone marrow colonies were screened for the transgene. At one month, 8-78% of colonies contained the transgene. At six months, 4-10% of colonies contained the transgene.
February 16, 1999	**9804-246 Yoo *et al.***	**A Multicenter Phase II Study of E1A Lipid Complex for the Intramural Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma** **Amendment:** One new investigator/site is added. The new investigator is Daniel E. Kenady, M.D. at the University of Kentucky, Lexington, Kentucky.
February 18, 1999	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendments:** Minor amendments have been made that include an additional blood test for toxicity to

		administered medication. In addition, the exclusion criteria have been modified to allow patients who have had another malignancy, but have been free of disease for at least five years, to be enrolled.
February 18, 1999	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendments:** Minor amendments have been made that include preliminary and follow-up tests. In addition, the exclusion criteria have been modified to allow patients who have had another malignancy, but have been free of disease for at least five years, to be enrolled. Also, patients who have had more than one therapy for their current disease are now eligible.
February 18, 1999	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** Two new investigators/sites are added. The new investigators are: 1) Lynn M. Schuchter, M.D. at the University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania and 2) Albert Deisseroth, M.D., Ph.D. at Yale University School of Medicine, New Haven, Connecticut.
February 18, 1999	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives** **Amendment:** One new investigator/site is added. The new investigator is Albert Deisseroth, M.D., Ph.D. at Yale University School of Medicine, New Haven, Connecticut.
February 18, 1999	**9503-103 Morgan and Walker**	**Gene Therapy for AIDS Using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant REV Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins** **Update:**

		As part of NIAID-IRB's continuing review, changes have been made to the Informed Consent Document.
February 19, 1999	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site is added. The new investigator is Paolo A. Paciucci, M.D., at Mount Sinai Medical Center, New York, New York.
February 23, 1999	**9811-270 Hanna *et al.***	**Phase II Study of the Safety, Efficacy, and Effect on Quality of Life of Allovectin-7 Immunotherapy for the Treatment of Recurrent or Persistent Squamous Cell Carcinoma of the Head and Neck** **Amendment:** One new investigator/site is added. The new investigator is Gregory T. Wolf, M.D., at the University of Michigan Medical Center, Ann Arbor, Michigan.
February 25, 1999	**9802-234 Thompson *et al.***	**A Controlled, Randomized Phase III Trial Comparing the Response to Decarbazine with and without Allovectin-7 in Patients with Metastatic Melanoma** **Amendment:** One new investigator/site is added. The new investigator is Frank R. Dunphy, M.D., at Saint Louis University Health Sciences Center, St. Louis, Missouri.
March 12, 1999	**9707-204 Hickstein**	**Retrovirus-Mediated Transfer of the cDNA for Human CD18 into Peripheral Blood Repopulating Cells of Patients with Leukocyte Adherence Deficiency** **Amendments:**

		Dr. Thomas R. Bauer, University of Washington School of Medicine (original trial site) is now listed as a co-principal investigator. Two major changes and several minor changes have been made to the clinical protocol and where appropriate to the informed consent/assent documents.All of these changes have received IRB approval and FDA authorization. No patients were enrolled before all of these changes were implemented. The two major modifications are: 1) inclusion of moderate (as defined by 2 to 6% of normal CD11/CD18 levels) leukocyte adherence deficiency patients and 2) the lower age limit has been dropped from eight to four years of age.
March 16, 1999	**9611-165 Rosenberg**	**Phase I Trial in Patients with Metastatic Melanoma of Immunization with a Recombinant Fowlpox Virus Encoding the gp100 Melanoma Antigen** **Amendment:** Amendment for the intravenous administration of a fowlpox vector containing gp100. This amendment was received only after an inquiry from ORDA regarding previous systemic fowlpox administration to Dr. Rosenberg. ORDA made this inquiry during the RAC's initial review of protocol 9902-292, which was submitted on February 24, 1999. Intravenous fowlpox administration is one of the two proposed routes of administration in protocol 9902-292. At the time of submission of protocol 9902-292, a protocol calling for intravenous fowlpox administration had not been submitted to NIH RAC. The amendment for protocol 9611-165 to allow for intravenous fowlpox administration was approved by the IRB on December 7, 1998 and by the IBC on April 8, 1999.
March 23, 1999	**9902-287 Schiller**	**Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage** **Amendment:** One new investigator/site is added. The new investigator is David P. Carbone, M.D., at Vanderbilt University Medical Center, Nashville, Tennessee.

April 5, 1999	**9804-245 Moss**	**A Phase I Study of Aerosolized tgAAVCF for the Treatment of Cystic Fibrosis Patients with Mild Lung Disease** **Amendments:** 1) Minor amendment has been made that adjusts the volume of the aerosol for vector delivery to a maximum of 10ml. This change was done to attempt to reduce the time needed for vector delivery. 2) One new investigator/site is added. The new investigator is MoiraAitken, M.D., at the University of Washington Medical Center, Seattle, Washington.
April 6, 1999	**9806-259 Figlin *et al.***	**Phase II Study of Direct Gene Transfer of IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients withMetastatic Renal Cell Carcinoma** **Amendment:** One new investigator/site is added. The new investigator is RonaldBukowski, M.D., at the Cleveland Clinic Foundation, Cleveland, Ohio.
April 16, 1999	**9812-277 Amado**	**A Phase I/II Study in HIV-1 Infected Patients Infused with CD4+ Thy+ HematopoieticStem Cells (HSC) from G-CSF Mobilized Peripheral Blood Retrovirally Transduced with RevM10 or RevM10/Antisense Pol 1** **Amendment:** Three new investigators/sites are added. The new investigators are:1) MatthewCarabasi, M.D. at the University of of Alabama at Birmingham, Birmingham, Alabama; 2) Susan Swindells, M.D. at the University of Nebraska Medical Center, Omaha, Nebraska; and 3) David T. Scadden, M.D. at the Massachusetts General Hospital, Boston, Massachusetts.

April 19, 1999	**9806-261 Amado and Yuen**	**A Phase I/II Study of the Safety and Feasibility of RevM10 or RevM10Antisense Pol 1 Transduced Hematopoietic Stem Cells (HSC) in HIV-1 Related Non-Hodgkin's Lymphoma Patients Already Being Treated with High Dose Chemotherapy and Peripheral Blood Stem Cell Support** **Amendment:** Two new investigators/sites are added. The new investigators are:1) MichaelLill, M.D. at Cedars-Sinai Medical Center, Los Angeles, California; and 2) David TScadden, M.D. at the Massachusetts General Hospital, Boston, Massachusetts.
April 26, 1999	**9503-103 Morgan and Walker**	**Gene Therapy for AIDS Using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant REV Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins** **Amendment:** Use of slightly modified retroviral vectors that no longer express functional proteins from the bacterial gene encoding neomycinphosphotransferase.
May 7, 1999	**9804-246 Yoo *et al.***	**A Multicenter Phase II Study of E1A Lipid Complex for the Intramural Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma** **Amendments:** 1) Dr. Joseph Valentino is added as a co-principal investigator at the University of Kentucky. 2) Review of the results from the phase I trial employing E1A lipid complex suggested tha a patient with adenocarcinoma had a positive tumor response. Therefore the eligibility criteria for this phase II study will be broadened to allow for enrollment of patients with other types of head and neck region tumors, not just squamous cell carcinomas.
May 7, 1999	**9904-305 Baynes**	**A Phase I Study of Infused Mobilized, Autologous Peripheral Blood Progenitor Cells, Which Have Been Incubated with a Recombinant Adenovirus-Wild-Type p53**

		Construct (SCH 58500) to Purge Any Contaminating Breast Cancer Cells, As Stem Cell Support After High-Dose Chemotherapy in Patients with Breast Cancer Metastatic to Bone and Bone Marrow **Amendment:** Maximum tolerated dose has been redefined from two failures of engraftment to one failure.
May 10, 1999	**9806-261 Amado *et al.***	**A Phase I/II Study of the Safety and Feasibility of RevM10 or RevM10Antisense Pol 1 Transduced Hematopoietic Stem Cells (HSC) in HIV-1 Related Non-Hodgkin's Lymphoma Patients Already Being Treated with High Dose Chemotherapy and Peripheral Blood Stem Cell Support** **Amendment:** One new investigator/site is added. The new investigator is Matthew Carabasi, M.D. at the University of Alabama at Birmingham, Birmingham, Alabama.
May 10, 1999	**9509-124 Curiel and Alvarez**	**A Phase I Study of Recombinant Adenovirus Vector-Mediated Delivery of an Anti-erbB-2 Single Chain (sFv) Antibody Gene for Previously Treated Ovarian and Extraovarian Cancer Patients** **Update:** The IND for this trial; as of April 13, 1999; was inactivated due to completion of patient accrual. A total of 15 patients were treated in five cohorts. However, due to a limitation in clinical grade vector, only one patient was treated at the highest dose level (1×10^{11} pfu). A dose limiting toxicity was not observed. Adverse events were all mild in nature, none grade 3 or 4. Thirteen of the fifteen patients were evaluable for a response to the treatment. Five of the patients experienced stable disease, whereas eight experienced disease progression. None of the patients died within the eight week post-vector evaluation period. Seven patients have died, all due to progressive disease.
May 11,	**9804-244**	**A Phase I Study Using Direct Combination DNA Injections for the Immunotherapy**

1999	**Walsh**	**of Metastatic Melanoma** **Amendments**: Minor amendments have been made to the timing of a pre-study test and the exclusion criteria.
May 17, 1999	**9706-196 Smith and Dinauer**	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** **Amendments:** Minor amendments have been made including additional blood tests to help clarify the results from other tests. Other administrative changes have been made.
May 17, 1999	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase** **Amendments:** Minor amendments have been made. For example, revisions that reflect changes in the FDA definition of adverse experience have been made.